Bacteremia caused by multi-resistant Gram-positive microorganisms

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INTRODUCTION

The occurrence of bloodstream infections (BSI) has increased among hospitalized patients over the last decade [1]. In recent years Gram-positive bacteria have emerged as important pathogens, both in the community and hospital. To compound these problems, antimicrobial resistance long considered the domain of Gram-negative bacteria, is being increasingly exhibited by Gram-positive strains [2].

Three etiologic factors have made major contributions to the increase in the relative frequency of Gram-positive BSI among all nosocomial infections. These include shifts in patient demographics, the increased use of intravascular and other prosthetic devices, and the increased use of broad-spectrum antibiotics, such as the cephalosporins. To a lesser extent, a change in defining criteria for coagulase-negative staphylococcal bloodstream infection may also have contributed to this trend. However, the increase in the number of hospitalized patients at risk for such infections may be the single most important factor. Of the 35 million patients admitted to US hospitals each year, at least 2.5 million will develop a nosocomial infection, of which 250 000 will be bacteremic episodes. The attack rate for nosocomial BSI range from 1.3 to 14.5 per 1000 hospital admissions, varying with the type of population studied, size of hospital, length of hospital stay and the ward location of the patient within a hospital [3].

Since the early 1980s the contribution of BSI to the total incidence of nosocomial infections has increased at the same time as the relative proportion of BSI caused by Gram-positive organisms has increased [1,4–11]. Table 1 shows the changing patterns of bacteremic isolates as reported to Microbe Base (Glaxo–Wellcome) National Computerized Data Base comprising in excess of 1.7 million patient records downloaded from the laboratory computer system of 61 participating UK laboratories over ten years [12]. The ratio of Gram-positive bacterial isolates to Gram-negative strains has increased from 1.5:1 to 4.3:1 between 1986 and 1998.

The increase in the proportion of BSI caused by Gram-positive bacteria has been directly related to hospital size and to the treatment environment, which is typically more complex in teaching hospitals than in non-teaching hospitals. Table 2 shows the most common species isolated from blood cultures in the United Bristol Hospitals Trust (UBHT), a tertiary referral complex of hospitals. As can be seen, Gram-positive isolates predominate in immunocompromised patients when compared with the overall hospital population and in the care of the elderly, where Gram-negatives predominate.

Banerjee et al. [5] reported on a ten-year period, between 1980 and 1989 when >25 000 primary bloodstream infections were identified by 124 NNIS hospitals performing hospital-wide surveillance. Significant increases occurred ($p<0.0001$) within each hospital stratum—small non-teaching (<200 beds), small teaching (<500 beds), large non-teaching (>200 beds), large teaching (> 500 beds)—in overall BSI rates

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Table 1 Distribution % of bacteremia isolates as reported to Microbe Base between 1986 and 1998 (total no. of bacteremia isolates = 396433)

	1986	1990	1994	1998
Coag.-neg. staph.	30.2	39	49.2	48.8
E. coli	19.3	14.8	12.8	8.2
Staph. aureus	15.2	10.7	9.7	12.5
S. pneumoniae	3.3	4.8	3.2	3.5
Enterococci	2.9	2.2	2.7	6.1
Klebsiella spp	2.9	2.4	2.9	3.0

Table 2 Blood cultures (UBHT) total patient episodes

	% occurrence		
	Whole hospital (n=560)	Immuno-compromised (n=110)	Care of Eldery (n=150)
E. coli	21	11	38
Coag. neg. staph.	16	50	0
S. pneumoniae	9	0	14
Staph. aureus	7	2	7
Enterococci	7	5	7
MRSA	6	2	11
Yeasts	1	7	0

and the BSI rate due to coagulase-negative staphylococci (increases 161–754%); *Staphylococcus aureus* (increases 122–283%) and enterococci (increases 120–197%). By contrast, the BSI rate due to Gram-negative bacilli remained constant.

Pittet et al. [13] studied the effect of nosocomial BSIs in critically ill patients and estimated the attributable mortality rate to be 35%. They calculated that the extra stay in hospital was 24 days and the extra stay in intensive care units was eight days when compared with matched controls (n=41). The extra cost was calculated to be on average 40000 US dollars per survivor. The Office of Technology Assessment of the US Congress in their report [14] calculated the costs of bacteremia caused by some antibiotic-resistant strains. The cost of MRSA bacteremia was calculated at 10 million US dollars; VRE bacteremia 2.6 million dollars; and methicillin-resistant coagulase-negative staphylococcal bacteremia to be 56 million dollars.

Neutropenic patients are a group of patients at particular risk of BSI from Gram-positive bacteria [15]. In the eight-year period between EORTC trials I (1973–1976) and XI (1993–1994) the percentage of Gram-negative bacteremia decreased from 71% to 31%; whilst that of Gram-positive bacteremia increased from 29% to 69%. Coagulase-negative staphylococci have been recognized as the leading pathogen causing nosocomial bacteremia in general, accounting for about one-quarter of all bloodstream infection [3] as well as in the neutropenic host. Viridans streptococci, initially considered to be pathogenic only in the setting of infective endocarditis, have now become prominent as one of the leading organisms to cause bacteremia in neutropenic patients. Enterococci are becoming an increasingly common cause of hospital-acquired bacteremia, being cited as the third most common pathogen in some series [16]. In addition to increasing its numbers there has been a change in the species-causing infection, with *E. faecium* increasingly taking over from *E. faecalis* as the predominant cause of serious infection [17]. Hand in hand with the increasing frequency has been the development of antibiotic resistance, especially to the glycopeptides. Resistance occurs when strains of enterococci produce structurally related ligases (Van A and Van B) which synthesize altered precursors that bind the glycopeptides with a reduced affinity, altering cell wall production in the presence of the antibiotic [18]. Bacteremia is often associated with fatal outcome, although this may reflect the relationship between bacteremia and severe underlying disease, rather than any particular virulence of the organism.

The European Prevalence of Infection in Intensive Care (EPIC) Study was conceived as a point prevalence study of infection [19]. Of the 10038 patients, a total of 4501 had one or more infections on the EPIC Study day: 13.7% (1,376 cases) were community acquired, 9.7% (975 cases) were hospital acquired, 20.6% (2064 cases) were ICU acquired and in a small minority of cases no information was given on where the infection was acquired. Infections acquired in ICUs therefore constituted almost half (45.9%) of all cases of infection for which a source of acquisition was indicated. In most of these cases, a single infection was present; only 25.6% of ICU-infected patients had two or more infection. Bacteremia was reported in 12% of ICU-acquired infections [20]. The results of the EPIC study are in line with previous reports that have documented the emergence of coagulase-negative staphylococci as increasingly important nosocomial ICU pathogens, especially in bloodstream infections [7]. These bacteria were the most commonly isolated organisms in laboratory-confirmed ICU-acquired bloodstream infections. Coagulase-negative staphylococci were generally reported to be highly resistant to antimicrobial agents, although they generally remained sensitive to vancomycin and (to a lesser degree) teicoplanin. The increase in coagulase-negative staphylococcal bloodstream infections has been attributed to the increasing use of intravascular catheters, with subsequent colonization of

the catheters and the development of invasive disease [7]. The findings of the EPIC Study are in accordance with this: 67% of patients who developed bloodstream infections in an ICU had intravenous catheters, 61% had arterial catheters, and 88% had central venous pressure lines [20].

As mentioned previously, the increase in incidence of Gram-positive bacteria as etiological agents of BSI has been mirrored by problems associated with an increase in antimicrobial resistance [21]. Heterogeneous resistance to glycopeptides in strains of MRSA have been reported [22,23]. Viridans streptococci which were previously universally susceptible to penicillin have been increasingly penicillin-resistant over the past decade [24]. Strains of coagulase-negative staphylococci, which are relatively resistant to glycopeptides, have been described in several clinical settings [25]. Since the first description of vancomycin-resistant enterococci by Uttley et al. [26] VRE have become well established nosocomial pathogens worldwide. There is also the problem for the explosive development of macrolide resistance in streptococci. The prevalence of macrolide resistance reached 60–70% in Japan and 60% in Spain [21]. A recent study in Finland has shown a direct correlation between the amount of macrolide usage and the emergence of erythromycin-resistant strains of *S. pyogenes* in Finland [27,28]. Perhaps of even greater concern is the potential for the emergence of macrolide resistance in penicillin-resistant strains of *Streptococcus pneumoniae*. Although the overall prevalence of macrolide resistance in *S.pneumoniae* in Europe and the United States is in the relatively low range of 5% to 10% [29], the prevalence of macrolide resistance in penicillin-resistant pneumococci is considerably higher, nearing 20% or more in some studies [29]. These developments warrant careful observation over the coming years, representing the increasing problems caused by antibiotic-resistant Gram-positive cocci.

COAGULASE-NEGATIVE STAPHYLOCOCCI

Coagulase-negative staphylococci are the most common cause of foreign body device infection and nosocomial bacteremia. Because of the expanding use of intravascular catheters and prosthetic devices, this problem continues to grow at an alarming rate [3,5,30–33].

There are increasing numbers of immunocompromised and critically ill patients dependent in their care on vascular catheters, such as neutropenic patients with cancer and long-term central venous catheters, or critically ill neonates with umbilical catheters. These patients are all prone to contract coagulase-negative staphylococcal bacteremia either from the skin via the IV catheters or gastrointestinal tract [34]. Such organisms have been reported as the most common cause of bacteremia in leukaemic patients and up to 75% of all nosocomial bacteremia in a neonatal intensive care unit [35]. Risk factors specific to coagulase-negative staphylococci as causes of nosocomial bacteremia include:

- presence of intravascular catheters
- length of hospital stay
- use of intravenous lipids in total parenteral nutrition
- severity of acute illness as measured by APACHE or SAPS scores
- low birthweight
- underlying disease
- neutropenia

Fidalgo et al. [36] found an associated overall death rate of 36.9% in cases of coagulase negative staphylococcal BSI. Underlying disease, hemodynamic status, neutropenia, immunosuppressive therapy and incorrect antimicrobial therapy were all statistically significant parameters in relation to mortality.

Although recognized as true pathogens, the most frequent encounter by clinicians is as a culture contaminant. In a large Spanish study [36], the results of 31 000 blood cultures taken between 1982 and 1987 in a large tertiary referral hospital were reviewed. Of the 5 198 positive cultures 48% yielded CNS of which 87% were considered contaminants. At present we lack a standard method for differentiating between CNS as true pathogens and when it occurs as a culture contaminant. It has been suggested that molecular typing methods may help differentiate between the two groups, but they are not generally available and results are not available in the early treatment period [37]. In contrast to their infrequent role as a cause of native valve endocarditis (1–3%), CNS are the most common bacteria infecting prosthetic cardiac valves, (30–50%), occurring within the first 12 months following surgery [38].

Two properties may explain the association of bacteremia with the use of indwelling intravascular catheters: the ability to adhere to foreign bodies and artificial surfaces due to adhesins and the production of extracellular glycocalyx (slime) [39]. A significant proportion of coagulase-negative staphylococci bacteremia could be avoided by the prevention of device-associated nosocomial infection [39,40–43], using catheters impregnated with metals, disinfectants or antibiotics.

At the same time as an increase in prevalence has occurred, an increase in antibiotic resistance has also happened [2,21]. Coagulase-negative staphylococci from nosocomial infections, especially *S. epidermidis* and *S. haemolyticus*, are usually resistant to multiple anti-

biotics, with more that 80% resistant to methicillin [44]. In addition to β-lactam agents, many coagulase-negative staphylococcal strains are resistant to macrolides, aminoglycosides and lincosamides. Strains of *S. haemolyticus* are especially resistant to teicoplanin and also, though less frequently, to vancomycin [25,45]. However, at the moment the glycopeptide antibiotics such as vancomycin and teicoplanin, together with rifampicin, are the mainstay of the treatment of coagulase-negative staphylococcal bacteremia. The efficacy of fluoroquinolones in the treatment of such infections has yet to be accurately delineated, but resistance in colonizing strains of coagulase-negative staphylococci rapidly emerges in patients receiving ciprofloxacin [46].

STAPHYLOCOCCUS AUREUS

In most cases, *S. aureus* bacteremia is the consequence of invasion from a local infection. Such infected foci can be categorized as extravascular foci, such as cellulitis, surgical wound infection, osteomyelitis, pneumonia; intravascular foci, such as intravascular catheters; and presumed intravascular foci such as intravenous drug abusers [47]. However, in about 30% of bacteremic patients, no focus of infection can be found. The diagnosis of acute endocarditis, caused by *S. aureus*, carries an ominous prognosis with a mortality of some 60% [47]. Patients colonized by MRSA are at risk of developing bacteremia which can lead to significant morbidity and mortality [48]. It has been estimated that bacteremia occurs in 1–3% of nosocomial MRSA bacteriuria [49]. Risk factors for MRSA bacteremia include: [4,48,50–52]

- MRSA colonization
- severe underlying disease
- poor clinical prognosis
- prolonged length of hospital stay
- immobilization and age
- previous broad-spectrum antibiotic use
- previous surgery
- selective gut decontamination

Among cases of *S. aureus* bacteremia reported in England and Wales [53,54] the proportion due to MRSA has increased significantly from 1.6% in 1989 to 13.2% by 1995, 21.1% in 1996 and 31.7% in 1997. At the same time, there were significant increases in resistance to erythromycin (7.5% to 18.7%); gentamicin (2.5% to 5.3%) and ciprofloxacin (2.9% to 23.1%). Rates of multi-resistance to these unrelated drugs were much higher amongst MRSA isolates, than methicillin-sensitive strains. In a report from Brazil, Conterno et al. [55] found the prevalence of MRSA bacteremia varied from 5% to 50% depending on the characterization and size of the hospital. In the United States approximately 25% of staphylococcal bacteremia are caused by MRSA, and significantly higher rates have been reported from hospitals where MRSA is endemic [11]. By comparison, Denmark shows an incidence of only 0.1% MRSA in staphylococcal bacteremia [56].

Uncertainties remain about the contribution of methicillin resistance to morbidity and mortality associated with bacteremia caused by *S. aureus*. Romero-Vivas et al. [57] showed that nosocomial bacteremia due to MRSA was associated with a three–fold higher mortality than MSSA BSI after adjustment for several risk factors. However, Harbarth et al. [40] found that MRSA had no significant impact on patient outcome as measured by in-hospital mortality after adjustment was made for major confounders. French et al., from Hong Kong [58], showed that MRSA bacteremia had a poor prognosis, especially when not treated with suitable antibiotics. They showed that five (14.8%) of 35 patients with MRSA bacteremia treated with vancomycin died. Of 47 patients with MRSA bacteremia treated with antibiotics other than vancomycin, 28 (60%) died. Vancomycin thus remains the first line drug of choice for MRSA bacteremia, the findings of Hiramatsu and others notwithstanding [22,23]. Teicoplanin is the alternative glycopeptide but must be given in high doses, because of the high failure rate associated with a single loading dose of 400 mg, followed by 200 mg daily [59], while 6 mg/kg body weight, or 400 mg daily, remains effective. A minimum course of four weeks is mandatory.

There is little convincing evidence to suggest that MRSA is less pathogenic, especially in the vulnerable patient. The outcome of MRSA infections is at least similar to that of MSSA infections, when mortality is corrected for underlying disease. In a comparison of ventilator-associated pneumonia caused by MRSA and MSSA there was a higher incidence of bacteremia and septic shock in patients with MRSA and, when allowing for other variables, higher mortality [60]. In a prospective study of 84 cases of MRSA bacteremia compared with 100 cases of MSSA bacteremia, statistical analysis showed that methicillin-resistance was independently associated with death due to *S. aureus* bacteremia, and the mortality was three times higher in patients in the MRSA group [57]. They also found that patients acquiring MRSA in intensive care had a longer duration of stay, higher overall mortality and required more antibiotics. Burns units are also places that provide a fertile environment for MRSA where bacteremia may be a serious complication following extensive colonization [61].

Nosocomial *S. aureus* bacteremia, particularly MRSA, is a major source of preventable morbidity and mortality, which can only be addressed by an improved infection control programme for MRSA, the proper use of antibiotics and the attention to central line catheter use [62].

ENTEROCOCCI

Enterococci are opportunistic pathogens of low virulence whose ability to cause bacteremic disease is closely linked to the compromised host's absence of local or systemic defences. Vancomycin-resistant enterococci were first reported from London in 1986 [26], since when they have become a worldwide problem [63]. Vancomycin resistance increased from 0.3% in 1988 to 14.4% by 1996 in United States bacteremia enterococcal isolates [17,64]. Enterococci are now consistently in the top three of US nosocomial bloodstream infections. *Enterococcus faecium* is increasing as a percentage of these isolates [65]. The high rates of morbidity observed in many patients with enterococcal bloodstream infections, has led many to question whether enterococci can cause disease independently, other than in cases of SBE. There are studies which show that bloodstream infections caused by vancomycin-susceptible enterococci were associated with an attributable mortality, even when adjusted for underlying disease [66,67]. Does antimicrobial resistance in enterococci therefore lead to an adverse clinical outcome? In two studies marginal increases in mortality were found in cases caused by aminoglycoside-resistant enterococci [68,69]. Noskin et al. [65] also reported a higher infection-attributable mortality with *E. faecium* bacteremia than with *E. faecalis* bacteremia. The clinical effects attributable to glycopeptide resistance have varied in those studies that have compared clinical outcomes between VRE and VSE [70–76]. The lack of co-morbidity data in some studies, such as the NNIS, makes it difficult to estimate that portion of the mortality which is due to the enterococcal infection. The NNIS data [77] collected between 1989 and 1993 showed a significantly higher crude mortality for VRE when compared with VSE bacteremia (36.6% versus 13.6%, $p<0.0001$). Higher morbidity and mortality rates related to enterococcal bacteremia have been found in studies in which the patients had compromised host defences or serious illnesses—transplant patients, neutropenic patients and those in intensive care units [71–73].

Risk factors for systemic infection by VRE include [64,70,78,79]:

- prolonged hospitalization especially in intensive care units
- severe underlying disease—immunocompromised status, neutropenia, organ transplantation, renal failure/dialysis
- prior nosocomial infection
- intra-hospital patient transfer
- prior colonization with VRE
- prior antibiotic usage, especially with third generation cephalosporins and the carbapenems.

During the last two decades there have been two major landmarks in acquired antibiotic resistance amongst the enterococci. First, high level aminoglycoside resistance and, secondly, high glycopeptide resistance. There have been several glycopeptide-resistance phenotypes described, of which Van A and Van B are the most common [18]. Antibiotic resistance has important implications for the management and outcome of cases of enterococcal bacteremia. No optimal drug regimen for the treatment of VRE bacteremia has been found. Some VRE strains remain susceptible to ampicillin, which can therefore be used therapeutically. However, infections due to organisms, usually *E. faecium*, with both high level penicillin and vancomycin resistance, are much more of a challenge. Combination therapy with vancomycin plus gentamicin plus ampicillin have demonstrated efficacy in animal models, but their clinical effectiveness remains to be demonstrated [80]. Despite the fact that VRE of the Van B phenotype remain susceptible to teicoplanin in vitro, clinical efficacy with teicoplanin has not been universally successful, giving rise to the development of teicoplanin resistance [81]. Other treatments include use of tetracyclines [82] and the new agent quinupristin/dalfopristin, an antibiotic only effective against *E. faecium*. In one report a combination of minocycline and quinopristin/dalfopristin was synergistic, with a success rate of approximately 50% in neutropenic patients with VRE bacteremia [63].

There are major differences in the epidemiology of vancomycin-resistant enterococci (VRE) between the United States and Europe. In contrast with Europe, VRE in the United States are resistant to many antibiotics, and there appears to be less genetic variability among these isolates. In comparison European VRE of human origin are usually susceptible to many other antibiotics and are highly polyclonal. These clinical isolates have the same susceptibility profiles as VRE isolated from animals. The differences in the spread of VRE between the United States and Europe might be explained by the over-consumption of glycopeptides and other antibiotics in American hospitals, and the use of avoparcin as a growth promoter in Europe [83].

Prevention is the best policy for the control of VRE and includes contact isolation, cohorting of

patients, isolation of colonized or infected patients and the appropriate use of glycopeptides and education of patients and staff. Strict handwashing is the most important and helpful recommendation [77].

STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae is a common pathogen and a major cause of morbidity and mortality. In the United States alone it has been calculated that each year *S. pneumoniae* accounts for half a million cases of pneumonia, 55 000 cases of bacteremia and 6 000 cases of meningitis [84]. In some reports on bacteremia, *S. pneumoniae* is the second most common cause of community-acquired bacteremia in adults [85]. Increasing resistance to pencillin is now a worldwide phenomenon [86] with rates as high as 25–40% in Spain, leading to mortality rates of 20–54% [87,88]. In a report by Martinez et al. [89] among the 57 strains isolated from either blood or CSF, 18 (31.6%) and 8 (14%), respectively, were intermediate or resistant to penicillin and 7 (12.3%) and 2 (3.5%), respectively, were intermediate or resistant to third-generation cephalosporins.

Death caused by severe pneumococcal disease is related not only to the patient's health, but also to features of the bacterium and antimicrobial therapy used [90]. In their study of 71 patients Gomez et al. [91] found the risk factors associated with penicillin-resistant pneumococcal bacteremia were:

- age >60 years
- severity of underlying disease
- previous lower respiratory tract infections
- previous use of β-lactam antibiotics

Of the 71 patients, there was a 20% mortality and the factors associated with death were age, rapidly fatal underlying disease, nosocomial acquisition, initial clinical status, neutropenia and inappropriate antibiotic treatment. The degree of penicillin resistance did not significantly influence the clinical course or mortality. This study did not confirm the differences in risk factors found between penicillin-susceptible and penicillin-resistant pneumococcal bacteremia as found by Pallares et al. [88] in a retrospective series—previous hospital stay, nosocomial acquisition or pneumonia during the previous year.

Does the degree of penicillin resistance affect the clinical outcome of the patient? In the study of Pallares et al. [88] they found a significantly higher mortality in the penicillin-resistant group (54%) compared with the susceptible group (25%). However, Gomez et al. [91] found the influence of the degree of penicillin-resistance on the clinical course was not significantly different between the two groups. Other authors believe that the degree of antibiotic resistance does not significantly influence the risk of death, which mainly occurs as a result of the severity of the underlying disease, the initial status of the patient and the type of antibiotic treatment used [30,85,90–92]. Inappropriate antibiotic treatment seems to be the main reason associated with a high mortality. In the treatment of the penicillin-resistant pneumococcal bacteremias, high doses of penicillin can achieve clinical and microbiological cure [88,91,93].

Pradier et al. have found striking differences in penicillin susceptibility amongst various European countries [94]. In their study, data on penicillin-resistance patterns, antibiotic use and mode of administration and treatment compliance in five European countries (France, Spain, Germany, Italy and the UK) were compared. High prevalence rates of penicillin-resistant pneumococcal disease have been reported in Spain and France, where antibiotics are widely prescribed, and overall in Europe, patient compliance with more than 50% of oral antimicrobial prescriptions is inadequate. The low prevalence of penicillin resistance in Germany and the UK coincides with lower antibiotic consumption and better treatment compliance in these countries. Recent attempts to raise public awareness and to restrict and improve indications for antimicrobial agents have resulted in decreased pneumococcal resistance in Hungary and Iceland, suggesting that pnuemococcal resistance can be reversed.

Apart from β-lactam resistance, resistance to other antibiotics such as macrolides, tetracyclines and chloramphenicol have simultaneously increased [95]. Treatment of serious invasive penicillin-resistant pneumococcal disease, including bacteremia, remains third generation cephalosporin antibiotics such as cefotaxime and ceftriaxone [96].

The increasing resistance of *S. pneumoniae* to antimicrobial agents is a major cause for concern. Although several therapeutic strategies are possible, local patterns of resistance must be considered. It is essential to determine the susceptibility of individual strains to penicillin and other antimicrobial agents that could be used for treatment. Communication between the clinician and the laboratory remains vital to determine the best therapeutic options. The recent recognition of cephalosporin-resistant strains emphasizes the need to determine susceptibility to cephalosporins. Laboratories should be aware of the recently proposed changes in the definition of cephalosporin resistance, and clinicians need to be aware how these changes affect the choice of antibiotic therapy. Until pneumococcal disease can be effectively prevented, by the use of better vaccines, we can expect resistant

pneumococcal infections to continue to pose therapeutic difficulties. Even with optimum antibiotic therapy, the mortality from pneumococcal bacteremia, usually with underlying pneumonia, has remained at about 25% [88]. The emergence of antibiotic resistance in *S. pneumoniae*, with its associated problems of treatment, has encouraged immunization against pneumococcal infection. The pneumococcal 23–valent polysaccharide vaccine is safe, but its protective efficacy is not certain; some studies and a meta-analysis of randomized controlled trials have shown rates of protection against pneumococcal bacteremia of 56–70% in the elderly [97].

VIRIDANS STREPTOCOCCI

Streptococci of the viridans group have long been considered to be minor pathogens, except in subacute bacterial endocarditis. In the pre-antibiotic era, viridans streptococci accounted for 75% of cases of infective endocarditis [98]; in the current era their frequency has declined to 30%–40% [99]. For some years these bacteria have been the cause of serious bacteremia in neutropenic patients receiving intensive chemotherapy [100]. These infections can lead to severe complications such as endocarditis, respiratory distress syndrome, even shock [101], with association mortality rate of between 10% and 30%. Principal risk factors [101,102] for these infections are:

- profound neutropenia
- antibiotic prophylaxis and co-trimoxazole or quinolones
- use of H_2 receptor antagonists
- oropharyngeal mucositis.

Prevention of viridans streptococcal bacteremia in high-risk patients relies mostly on measures that minimize oral inflammation and decrease bacterial overgrowth. Use of prophylactic penicillin or vancomycin has been suggested, but is of questionable value and raises the spectre of selection of resistant strains [103]. Pfaller et al. [10] found in the SCOPE National Surveillance Program that, in addition to penicillin-resistant strains of viridans streptococci from bacteremias, there was also resistance to ceftriaxone (31%), erythromycin (51%) and 15% of strains were also resistant to ceftriaxone and erythromycin.

STREPTOCOCCUS PYOGENES

During the past decade there has been an increase in the prevalence of reported cases of group A streptococcal bacteremia. Many of the patients have been previously healthy adults between the ages of 20 and 50 years. There has been an apparent increase associated with intravenous drug abusers [104,105] and nosocomial outbreaks in homes for the elderly [106,107]. Diabetes mellitus and peripheral vascular disease are important risk factors for the elderly where skin is the predominant portal of entry. Mortality ranges from 30 to 40% [108,109].

Despite 50 years of extensive and often indiscriminate use of penicillin ('sold over the counter' in many countries) for the treatment of infections due to *Streptococcus pyogenes*, the organism continues to remain exquisitely susceptible to this antibiotic. Indeed no clinical isolate resistant to penicillin has been identified, and a recently completed survey of the susceptibility to penicillin of *S. pyogenes* strains isolated over a period of 80 years has revealed no change in the activity of penicillin [110]. However, resistance to other antibiotics does occur and reports of significant numbers of erythromycin-resistant *S. pyogenes* have appeared especially from Japan [111], Finland [27,28] and Italy [112], usually associated with excessive macrolide consumption.

CORYNEBACTERIUM JEIKEIUM

Corynebacterium jeikeium is clinically regarded as the most important of the lipophilic *Corynebacterium* spp. These isolates were previously designated as CDC coryneform group JK bacteria [113], isolated from the skin of healthy people, mainly perineum and axilla. *C. jeikeium* can also be found as environmental contaminants in hospitals [114]. *C. jeikeium* has been found to be the causative microorganism in endocarditis, bacteremia, meningitis, osteomyelitis and other nosocomial infections. The risk factors for acquiring or developing serious disseminated infections include immunosuppression, prosthetic devices (especially long-term central venous catheters, such as Hickman or Broviac), prolonged stay in hospital and prior exposure to broad spectrum antibiotics. Subacute endocarditis caused by *C. jeikeium* is more commonly associated with prosthetic than with normal heart valves [115]. Most clinical strains are resistant to β-lactam agents, macrolides, lincosamides and aminoglycosides; some strains are susceptible, in vitro, to the glycopeptides, fluoroquinolones and tetracyclines [116].

DISCUSSION

The evolving dominant role of Gram-positive pathogens is related to the high proportion of neutropenic and otherwise immunocompromised patients in our hospitals; the widespread use of intravascular devices

together with urinary, peritoneal and ventricular indwelling devices in the management of a variety of diseases and the expanded use of drugs with activity directed against Gram-negative organisms [16]. The range of effective compounds that are available for prophylaxis and treatment of infections due to Gram-negative organisms is significantly greater that those available for the management of Gram-positive infections. This results in a selective advantage to several Gram-positive species in the initial establishment of colonization prior to infection. For instance, acquisition of ampicillin-resistant strains of enterococci have been associated with exposure to multiple antibiotics [117]. Increasing incidence of infection with Gram-positive species is also associated with increasing antimicrobial resistance in this group of organisms, and alarming reduction in the range of therapeutic agents for such an infection.

Infection control measures are a crucial element in preserving the effectiveness of currently available antimicrobial agents. Handwashing, improved hygiene and patient isolation have been identified as successful infection control measures. Purchasers and commissioning agencies for hospital services should put infection control and basic hygiene where they belong, at the heart of good hospital management and practice, and redirect resources accordingly. Such a policy will pay for itself quite quickly. Reduction in the bloodstream infection rates by multi-resistant Gram-positive bacteria, especially coagulase-negative staphylococci, is dependent upon strict adherence to published guidelines for insertion and maintenance of intravascular catheters, use of intravasculars only when necessary and advances in the design and constituents of intravascular catheters [39,42,118–120].

Determination of current resistance patterns and the most appropriate empirical antibacterial treatment is best achieved by bacterial surveillance [121]. This can be done in individual hospitals, nationally between hospitals and internationally between countries. Microbiological surveillance provides vital information on the pathogens isolated from patients, particular hospital environments, and other sources, together with common patterns of antibacterial susceptibility. Surveillance is likely to be of greatest benefit in environments such as intensive care units or transplant units including oncology, where patients are at particular risk of acquiring nosocomial infections. Other benefits include the early detection of antibacterial resistance in specific bacteria and a reduction in the inappropriate use of antimicrobial agents. Studies have shown that infection control measures, together with microbiological surveillance, can significantly reduce infection rates and hospital costs. However, currently the collection of bacterial susceptibility data is incomplete and comprehensive national and international data are not yet established or the information is not made widely available. The microbiology laboratory influences antimicrobial drug usage through its routine reports and through consultations between microbiologists and clinicians, but perhaps most importantly by providing continuing data collection and analysis [12]. This generally serves to reinforce exisiting hospital antibiotic policies, but can also identify emerging problems to be addressed as part of the continuing dialogue between microbiologists and clinicians. Such dialogue is essential if we are to avoid losing valuable antimicrobial agents to acquired bacterial resistance.

Development of a new antimicrobial agent costs c. £350 million, takes 7–10 years, and yields a product used for brief periods against targets prone to develop resistance, i.e. bacteria. The use of the new antibiotic may be restricted to delay resistance or to reduce costs. It is therefore easy to understand why pharmaceutical companies may prefer to invest their monies elsewhere, and the number of investigational new drug permits for antimicrobial agents issued by the FDA in the USA has fallen from 59 in 1993 to 12–22 in 1994–96.

Many antibacterial agents have been launched in the past decade, but all are derivatives of old classes, and since resistance to the old class is (often) widespread, there is also the potential for rapid development of resistance in the new agents. In the past 15 years no new class of antimicrobial agents has been licensed. However, several new compounds presently under development have activity against multi-resistant Gram-positive organisms such as MRSA and VRE (Table 3). The oxazolidonones and everninomycins are the first new classes of antimicrobial agents to be developed for almost two decades. However it should be stressed that the compounds listed in Table 3 are at the developmental stage and there is no guarantee that they will be marketed. In addition, judging from past history, there are no reasons to believe that antibiotic resistance will not occur with these new compounds [122].

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Table 3 New antibacterial agents under development as of 1998

Compound	Class	Activity against		
		MRSA	GRE	Pen^R Pneumococci
Oxazolidones e.g. linelozid	Novel	+	+	+
Dalfopristin/ quinupristin	Streptogramin	+	+	+
Everninomycin	Novel	+	+	+
LY333328	Glycopeptide	+	+	+
Glycylcyclines	Tetracycline	+	+	+
Novel quinolones	Quinolones	+	±	+

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